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ORIGINAL RESEARCH

Overlapping and distinct neural metabolic patterns related to impulsivity and hypomania in Parkinson's disease

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Abstract

Impulsivity and hypomania are common non-motor features in Parkinson's disease (PD). The aim of this study was to find the overlapping and distinct neural correlates of these symptoms in PD. Symptoms of impulsivity and hypomania were assessed in 24 PD patients using the Barratt Impulsiveness Scale (BIS-11) and Self-Report Manic Inventory (SRMI), respectively. In addition, fluorodeoxyglucose positron emission tomography (FDG-PET) imaging for each individual was performed. We conducted two separate multiple regression analyses for BIS-11 and SRMI scores with FDG-PET data to identify the brain regions that are associated with both impulsivity and hypomania scores, as well as those exclusive to each symptom. Then, seed-based functional connectivity analyses on healthy subjects identified the areas connected to each of the exclusive regions and the overlapping region, used as seeds. We observed a positive association between BIS-11 and SRMI scores and neural metabolism only in the prefrontal areas. Conjunction analysis revealed an overlapping region in the middle frontal gyrus. Regions exclusive to impulsivity were found in the medial part of the right superior frontal gyrus and regions exclusive to hypomania were in the right superior frontal gyrus, right precentral gyrus and right paracentral lobule. Connectivity patterns of seeds exclusively related to impulsivity were different from those for hypomania in healthy brains. These results provide evidence of both overlapping and distinct regions linked with impulsivity and hypomania scores in PD. The exclusive regions for each characteristic are connected to specific intrinsic functional networks.

Keywords Impulsivity · Hypomania · Parkinson's disease · FDG-PET · Functional connectivity

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease which is characterized by progressive motor features including bradykinesia, rigidity, resting tremor and postural

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instability (Jankovic 2008). PD is also manifested by several non-motor symptoms including depression, anxiety, sleep disorders, hypomania, and impulsive behaviour (Chaudhuri et al. 2006). Although non-motor features significantly contribute to lower quality of life and severe disability in PD patients, their pathophysiology is less studied relative to motor symptoms (Opara et al. 2012). Hypomania and impulsivity are typical neuropsychiatric symptoms, which are associated with dopamine replacement therapy (DRT) or subthalamic deep brain stimulation (DBS) in PD (Dagher and Robbins 2009; Maier et al. 2014).

Impulsivity refers to behaviors consisting of risky decision-making and a lack of response inhibition in reaction to internal or external stimuli, disregarding potentially negative consequences for self or others due to neural disinhibition (Evenden 1999; Newman and Meyer 2014). High impulsivity is a risk factor for several mental health problems including impulse control disorders (ICDs), which are associated with severe behavioral symptoms including pathological gambling, compulsive shopping, binge eating and hypersexuality, which are common neuropsychiatric symptoms in PD (Ceravolo et al. 2009). Impulsivity may itself be seem as an umbrella term for different faces of 'premature' state outcomes (Dalley et al. 2011). ICDs, on the other hand, are complex behaviors that often involve reward-seeking behavior and tend to expand despite negative consequences (Probst and van Eimeren 2013). It is therefore important to conceptually distinguish between impulsivity and ICDs. On the other hand, high impulsivity has consistently been shown to be associated with ICDs and can therefore be conceptualized as an underlying substrate that may precede and predict risk of developing ICDs. The identification of neural substrates of increased impulsivity is therefore of specific importance in PD and should not be seen as entirely unrelated to ICDs.

To date, there are few neuroimaging studies exploring the underlying pathophysiology of impulsivity and ICDs in PD patients. For example, Cilia and colleagues revealed relatively increased blood flow in the orbitofrontal cortex (OFC), amygdala and globus pallidus in PD patients with ICDs (Cilia et al. 2008). Furthermore, it has been revealed that dopamine agonists may alter the OFC and rostral anterior cingulate cortex (ACC) activity in PD (van Eimeren et al. 2009, 2010). Recently, we have reported that higher impulsivity levels are associated with increased neural metabolism within the fronto-insular network in PD patients (Tahmasian et al. 2015c).

Hypomania and mania are also often observed in PD and are characterized by an abnormally elevated arousal and energy level, which varies in intensity, from a mild stage to a full symptomatic condition with over-activity, racing thoughts, and pressured speech (Maier et al. 2014). Positron Emission Tomography (PET) imaging in PD patients showed that hypomania was associated with strong asymmetrical cerebral activation preferentially involving the right hemisphere and was mediated by activation of the medial prefrontal cortex (mPFC), ACC and right middle temporal gyrus (Ulla et al. 2011; Chopra et al. 2012). Other PET imaging studies on non-PD patients with mania have revealed limbic structures such as the ACC and parahippocampal cortex, as well as the inferior frontal gyrus (Kupferschmidt and Zakzanis 2011; Blumberg et al. 2000). While impulsivity can be part of a hypomanic or manic state, the diagnosis of hypomania is not dependent on the presence of impulsive behaviors (Maier et al. 2014). In addition, high levels of impulsivity or ICDs can exist without hypomanic features (Voon et al. 2011b; Swann 2009).

Taken together, several studies considered impulsive behaviors to be linked with mania and hypomania in terms of predictive markers, risk factors, and behavioral features (Johnson et al. 2013; Swann 2009; Mason et al. 2012; Newman and Meyer 2014). However, the neural mechanisms of impulsivity and hypomanic symptoms, which are common in PD and related to DRT or DBS, are poorly understood. More knowledge about the brain maladaptation process related to impulsivity and hypomania in PD is needed, as it may lead to better targeted treatment strategies for patients in the future. Thus, we examined impulsive and hypomanic symptoms, as well as 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in 24 PD patients, in order to identify the overlapping and distinct patterns of regional metabolism related to such symptoms. Subsequently, we performed seed-based functional connectivity (FC) analyses on a dataset of 198 healthy subjects to find out the regions connected with the areas exclusive to impulsive and hypomanic symptoms.

Methods

Participants

We recruited 24 right-handed patients with idiopathic PD who met the United Kingdom Parkinson´s Disease Society Brain Bank criteria (Hughes et al. 1992) (mean age 66.29 ± 6.01 years) from the outpatient clinic for movement disorders, department of neurology, university hospital of Cologne. Every patient filled out an informed consent in accordance with the standard protocol for approved consent. Clinical records, medical histories and neurological examinations were considered for each of the patients including, among others, the Unified Parkinson´s Disease Rating Scale (UPDRS) part III (Fahn et al. 1987) which was used as an assessment for motor symptoms. Dyskinesia was assessed applying the UPRDS part IV (yes or no). The Hoehn and Yahr stage, assigned by two movement disorders specialists

(C.E., L.T.) was used to describe disease severity (Hoehn and Yahr 1967). Both of the scales were applied in the DRT OFF-state and their daily medication. To reach the OFF-state, patients abstained from DRT for at least 12 h or from controlled-released dopamine agonists for at least 72 h. Patients underwent neuropsychiatric testing on their regular daily medication. For further analyses, we calculated the LEDD of dopamine agonists according to the guidelines of the German Neurological Society (Diener and Putzki 2008). As it has been discussed that dopamine agonists may alter the activity of the prefrontal areas in PD, we chose dopamine agonist LEDD instead of total LEDD (van Eimeren et al. 2009, 2010; Tahmasian et al. 2015c). Results with total LEDD as a covariate were highly similar (not shown). Among other patient characteristics, we also recorded the side of disease onset and the disease duration since the first clinical diagnosis. We excluded patients suffering from current clinically relevant symptoms of depression ((BDI-II score > 19 (Beck et al. 1996; Kühner et al. 2007)) or severity of cognitive impairment (Mini Mental State Exam (MMSE) < 27 (Kessler et al. 2000)). Additionally, patients with other neurological diseases (trauma, stroke, brain tumor, epilepsy) were excluded. Of note, we used this dataset previously (Tahmasian et al. 2015c; Maier et al. 2016).

Psychological assessment

Impulsivity was measured by using the Barrett Impulsiveness Scale 11 (BIS-11) (Patton et al. 1995), which is the most often used self-report measure to assess impulsivity in the context of bipolar disorder (Newman and Meyer 2014). The BIS-11 consists of 30 four-point likert-type items representing the frequency at which impulsive behaviors occurred. In addition to the total score of BIS-11, three sub-scores reflecting attention, motor and non-planning impulsiveness can be calculated. On the other hand, hypomanic symptoms were assessed using the Self-Report Manic Inventory (SRMI) (Shugar et al. 1992; Kruger et al. 1997), a 48-item dichotomous questionnaire where the patient has to indicate whether the listed behaviors were present during the past 4 weeks. Patients were on their regular DRT, while completing these questionnaires.

FDG-PET data acquisition

FDG-PET images were generated with a high-resolution 24-detector ring PET scanner (ECAT EXACT HRRT, Siemens CTI, Knoxville, TN) with 207 transaxial image planes and 1.219 mm voxel size, as reported previously (Eggers et al. 2009). Subjects lay down in a supine position with low background noise and dimmed light at the same time of the day for all subjects. Scans were acquired after intravenous injection of 370 MBq of FDG. After injection of FDG, the tissue uptake of glucose increases in active areas of the brain, reflecting an indirect evidence of higher synaptic activity in a particular region (Klupp et al. 2015). Thus, FDG-PET imaging is a quantitative measurement of regional neural metabolism in the neuron-astrocyte functional units (Lucignani and Nobili 2010). Absolute quantification was performed by sampling arterialized venous blood. PET-images were acquired in 3-D mode and subsequently reconstructed and corrected for random artifacts, head motion, attenuation and scatter. The resolution parameters of the reconstructed images were 2.2 mm full width at half maximum (FWHM) in the center and 2.5 mm FWHM at 10 cm of-axis. Patients were on their regular DRT to minimize motion disturbances and to assess the subject's brain activity corresponding to daily life, which we correlated to questionnaires, reflecting everyday conditions while medicated.

FDG-PET data preprocessing and analysis

Preprocessing of images was performed with SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). First, we normalized the FDG-PET images to the standard stereotactical space using the standard PET template. After this, scans were smoothed with a 6 mm FWHM gaussian filter. For further details concerning FDG-PET image preprocessing, see our previous studies (Eggers et al. 2009; Maier et al. 2016; Tahmasian et al. 2015c).

To detect specific areas in which neural metabolism is related to one of the neuropsychiatric scores (BIS-11 for impulsivity and SRMI for hypomania), we performed two voxel-wise whole-brain multiple regression analyses across all the patients using SPM8. We also controlled for covariates of no-interest including age, gender, dyskinesia and LEDD for dopamine agonists as they have been shown to be highly correlated with hypomania and impulsivity (Maier et al. 2014; Abosch et al. 2011).

The height threshold $p < 0.005$ and an extended threshold of 140 voxels were used to show the significant results. In order to correct for multiple comparisons, we used an a-priori hypothesis driven "small volume correction (SVC)" approach (Worsley et al. 1996) with a sphere of 15 mm radius in SPM8 for the coordinates of the particular regions of interest in the prefrontal cortex including the dorsomedial PFC, dorsolateral PFC, ventrolateral PFC and precentral gyrus. We report the results of SVC as significant at $p < 0.05$ with family wise error (FWE) correction approach. The spheres were centered on coordinates reported previously (Soloff et al. 2008; Brown et al. 2015; Strakowski et al. 2011; Kluetsch et al. 2012; Winston et al. 2013; Lee et al. 2014) to avoid circularity in analysis (Kriegeskorte et al. 2009).

These steps were applied to generate both an "impulsivity-mask" and a "hypomania-mask" reflecting the relation

of BIS-11 and SRMI scores, respectively, to the FDG-PET scores.

Subsequently, we performed two voxel-wise whole brain analyses to identify the brain regions activated in both the impulsivity-mask and the hypomania-mask, and to identify the brain regions activated exclusively in each condition. To investigate the regions exclusively associated with impulsivity, we used the hypomania-mask with a more liberal threshold this time (uncorrected p-value 0.05). We applied this liberal hypomania-mask as an explicit mask on the impulsivity design created in the first step (described above), resulting in a mask of areas specific to impulsivity. The more liberal threshold of the exclusive mask increased the specificity of the persisting significant brain areas for impulsivity. This procedure was also applied to identify brain regions exclusively associated with hypomania.

The identified brain regions (overlapping and exclusive regions) were used as Volumes of Interest (VOIs) or seeds in further FC analyses in a dataset of healthy control resting state functional magnetic resonance imaging (rs-fMRI) images.

Resting- state fMRI data preprocessing and analysis

In order to investigate for different networks corresponding to impulsivity or hypomania, we performed rs-fMRI analyses using publically available neuroimaging data from the 1000 Functional Connectomes Project (FCP, http://fcon_1000.projects.nitrc.org/). Rs- fMRI images from the Cambridge-Buckner data set, including 75 male and 123 female subjects aged 18–30, were used. Participants were instructed to rest while remaining awake with eyes open in a 3T scanner and data was acquired using an echo-planar imaging sequence, with a repeat time (TR) = 3 s, echo time (TE) = 30 ms, time points = 119, slice number = 47, voxel size = 3 × 3 × 3 mm^3, and field of view (FOV) = 216 × 216. A high-resolution T1-weighted magnetization prepared gradient echo images (MPRAGE) were also obtained for each subject in order to spatially normalize the functional images.

FC analysis was performed using SPM8 and the Data Processing Assistant for Resting-State fMRI (DPARSF) version 4.0 (http://www.rfmri.org/DPARSF). Preprocessing steps of rs-fMRI data followed the previously published protocol (Tahmasian et al. 2015b, 2016). To avoid transient changes before reaching a steady state, the first 10 time points of each subject were discarded and then scans were processed with slice timing. Nuisance variables were regressed including white matter, CSF, and global signal. Head motion was corrected using the Friston 24 parameter model (Friston et al. 1996), as recent studies suggest higher parameter confound regression models are beneficial in removing motion artifacts (Power et al. 2015). Then, a T1-weighted normalization of the fMRI scans was performed into Montreal Neurological Institute (MNI) space, followed with band-pass filtering (0.01–0.1 Hz), and spatial smoothing with a 4× 4 × 4 mm Gaussian kernel to reduce spatial noise. Afterwards, we created spheres with a 4 mm radius centered at the peak coordinates of the VOIs identified in the preceding FDG-PET analysis. Whole-brain FC analysis was performed for each of the VOIs on the 198 rs-fMRI subjects (FWE corrected, $p < 0.05$). FC analyses were controlled for age and gender as covariates of no-interest.

Similarity coefficient

Sørensen–Dice similarity coefficients were calculated between pairs of binarized t-score maps representing intrinsic functional networks (Zou et al. 2004). These coefficients are reported as values between zero and one, where one reflects the complete anatomical overlap of the two networks. To assess the similarity and difference of the intrinsic functional networks objectively, we computed the Dice coefficients between the networks.

Results

Demographic and neuropsychiatric data

This study included 24 right-handed PD patients without clinically relevant symptoms of dementia, depression or ICDs. Patient characteristics are summarized in Table 1. The mean total BIS-11 score was 59.04 (higher score denotes a higher level of impulsiveness). For the SRMI,

Table 1 Patients' characteristics

Categories	Mean ± SD	Range
Gender (female/male)	8 / 16	–
Age (year)	66.29 ± 6.01	54–74
Duration since diagnosis (year)	8.75 ± 4.76	1–20
Hoehn und Yahr OFF	2.9 ± 0.80	2–5
Hoehn und Yahr ON	2.3 ± 0.88	1–5
UPDRS III OFF	33.21 ± 12.10	13–63
UPDRS III ON	23.25 ± 11.22	7–57
LEDD- total (mg)	697.36 ± 396.26	26-1560
LEDD- dopamine agonists (mg)	226.63 ± 161.70	0-640
MMSE	28.71 ± 1.12	27–30
BDI-II	10.83 ± 5.10	0–19
BIS-11 (total)	59.04 ± 12.07	21–78
SRMI	6.50 ± 4.84	0–17

Abbreviations: BIS barratt impulsiveness scale, *BDI-II* Beck Depression Inventory-2, *LEDD* levodopa equivalent daily dose, *MMSE* Mini-Mental state examination, *SRMI* Self-report manic inventory, *OFF* off-medication, *ON* on-medication, *UPDRS-III* Unified Parkinson's Disease Rating Scale-III, *SD* standard deviation

the mean score was 6.50 (higher score denotes a higher level of hypomania). There was a significant correlation between both of the scores ($r^2 = 0.502$, $p = 0.012$). Of note, data of the BIS-11 and the SRMI were normally distributed applying the Kolmogorov Smirnov test (for both $p = 0.200$).

Association between impulsivity and hypomania scores and neural metabolism

Voxel-wise multiple regression analyses across all patients revealed a positive association between impulsivity scores and neural metabolism in the medial part of the right superior frontal gyrus, right middle frontal gyrus and the left ACC ($p < 0.05$, Fig. 1a; Table 2a). On the other hand, a positive association between hypomania scores and neural metabolism was found in the right superior frontal gyrus, precentral gyrus, right middle frontal gyrus, and right paracentral lobule ($p < 0.05$, Fig. 1b; Table 2b). All FDG-PET analyses were controlled for age, gender, dyskinesia, and LEDD for dopamine agonists. There was no significant negative correlation between impulsivity and hypomania scores and neural metabolism.

Overlapping and exclusive regions of impulsivity and hypomania

Our conjunction analysis showed an overlapping region between the neural correlates of impulsivity and hypomania in the right middle frontal gyrus (Fig. 2a; Table 3a). Brain regions exclusively associated with impulsivity were found in the two regions in the medial part of the right superior frontal gyrus (Fig. 2b; Table 3b), whereas four regions related exclusively to hypomania were found in the right superior frontal gyrus, the right precentral gyrus and the right paracentral lobule (Fig. 2c; Table 3c). The two exclusive regions for impulsivity and four regions for hypomania, as well as one overlapping region was selected as seven VOIs for seed-based FC analyses in a dataset of 198 healthy controls (Fig. 3).

Intrinsic functional networks related to impulsivity and hypomania

FC was calculated for each of the seven mentioned VOIs in a dataset of 198 healthy controls. Based on the Anatomy toolbox (Eickhoff et al. 2005), the FC patterns of the impulsivity-related networks (VOIs 1 and 2), indicated that these two seeds are part of joint intrinsic functional networks comprising the mPFC, ACC, superior frontal

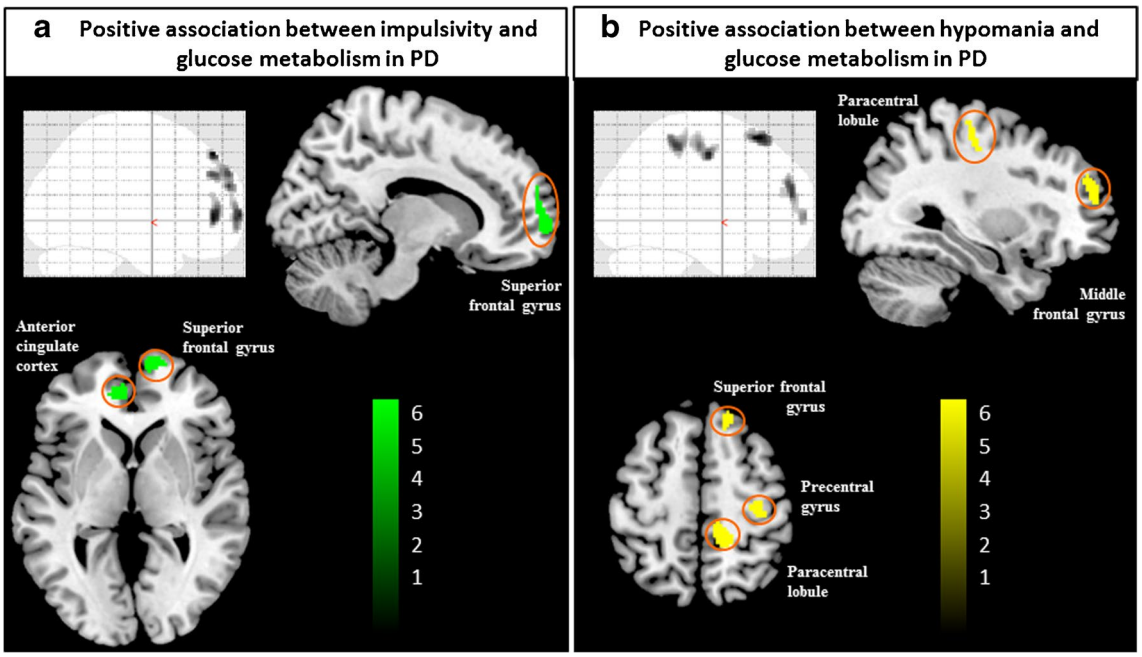

Fig. 1 Specific areas in which metabolic activity is related to impulsivity (green, **a**) or to hypomania (yellow, **b**) scores. A voxel-wise multiple regression analysis was performed to detect specific areas in which the metabolic activity is related to the BIS-11 scores for impulsivity in the right superior frontal gyrus and left ACC (**a**) and SRMI scores for hypomania in the right superior frontal gyrus, right precentral gyrus, right middle frontal gyrus and right paracentral lobule (**b**) Analyses were controlled for age, levodopa equivalent daily doses for dopamine agonists, dyskinesia and gender ($p < 0.05$, bars represent range of t-values)

Table 2 Regions with a positive association between neural metabolism and impulsivity (A) or hypomania (B) in PD

Anatomical region*	L/R	Cluster size	P-value (uncorrected)	P-value (SVC, FWE correction)	T-score	Peak (MNI)		
A. Positive association between neural metabolism and impulsivity in PD								
Superior frontal gyrus	R	295	0.007	0.009	5.43	22	46	48
Middle frontal gyrus	R	295	0.007	0.038	4.59	28	58	24
Superior frontal gyrus	R	295	0.007	0.009	4.45	24	58	32
Anterior cingulum	L	159	0.038	0.020	5.16	-6	46	0
Medial part of superior frontal gyrus	R	160	0.037	0.009	4.85	12	66	2
Medial part of superior frontal gyrus	R	160	0.037	0.009	3.03	10	58	24
B. Positive association between neural metabolism and hypomania in PD								
Superior frontal gyrus	R	150	0.045	0.023	5.78	14	26	60
Precentral gyrus	R	191	0.026	0.018	5.24	38	-12	48
Precentral gyrus	R	191	0.026	0.018	4.28	32	-20	54
Middle frontal gyrus	R	208	0.021	0.040	4.88	28	52	18
Superior frontal gyrus	R	208	0.021	0.023	3.99	24	62	2
Middle frontal gyrus	R	208	0.021	0.040	3.22	44	46	20
Paracentral lobule	R	186	0.028	0.046	4.87	12	-38	54

Abbreviations: SVC small volume correction, *FWE* family-wise error, *MNI* Montreal Neurological institute

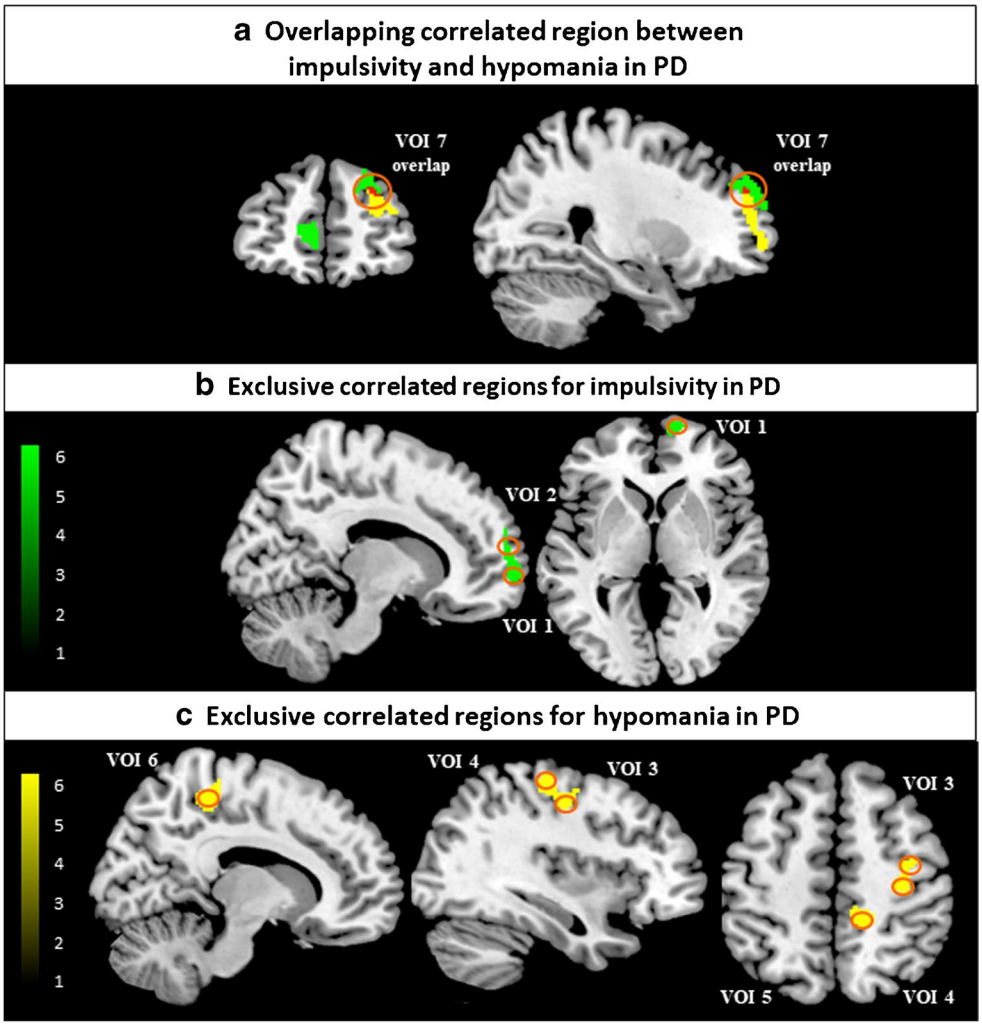

Fig. 2 Overlapping region (red) between areas related to impulsivity (green) and to hypomania (yellow) scores in the right middle frontal gyrus (**a**). Brain regions exclusively associated with impulsivity scores (green) were found in the medial part of the right superior frontal gyrus (**b**), whereas regions related exclusively to hypomania scores (yellow) were found in the right superior frontal gyrus, right precentral gyrus and right paracentral lobule (**c**) ($p < 0.05$, bars represent range of t-values)

Table 3 Overlapping (A) and exclusive regions associated with impulsivity (B) or hypomania (C)

Anatomical region	L/R	Cluster	P-value (uncorrected)	P-value (SVC, FWE correction)	T-score	Peak (MNI)		
A. Overlapping regions associated with both impulsivity and hypomania in PD								
Middle frontal gyrus	R	15	-	-	-	27	50	31
B. Exclusive regions associated with impulsivity in PD								
Medial part of superior frontal gyrus	R	149	0.043	0.009	4.85	12	66	2
Medial part of superior frontal gyrus	R	149	0.043	0.009	3.03	10	58	24
C. Exclusive regions associated with hypomania in PD								
Superior frontal gyrus	R	150	0.045	0.023	5.78	14	26	60
Precentral gyrus	R	191	0.026	0.018	5.24	38	-12	48
Precentral gyrus	R	191	0.026	0.018	5.28	32	-20	54
Paracentral lobule	R	186	0.028	0.046	4.87	12	-38	54

Abbreviations: SVC small volume correction, *FWE* family-wise error, *MNI* Montreal Neurological institute

gyrus, middle frontal gyrus, inferior frontal gyrus, posterior cingulate cortex, middle cingulate cortex (MCC), bilateral insula, bilateral angular gyrus, bilateral middle temporal gurus, and cerebellum. On the other hand, the FC patterns of the hypomania-related networks (VOIs 3–6), indicated that these four regions are part of intrinsic functional networks in the dorsomedial PFC including the bilateral precental and postcentral gyri, bilateral insula, rolandic operculum, lingual gyrus, cuneus, superior occipital gyrus, superior parietal gyrus, middle frontal gyrus, MCC, and thalamus. Moreover, the overlapping network was consisted of middle frontal gyrus, inferior frontal gyrus, ACC, MCC, insula, supramarginal gyrus, caudate, putamen, precentral gyrus, middle temporal gurus, and cerebellum (FWE corrected for multiple comparison, $p < 0.05$), controlled for age and gender) (Fig. 3).

Similarity and difference of the intrinsic functional networks

Subsequently, we tested the similarity and difference of the seven intrinsic functional networks and found that intra-group coefficients were higher than inter-group ones. In other words, impulsivity-related networks were similar to each other (Dice coefficient between VOI 1 and VOI 2 is 0.47). Similarly, hypomania-related networks were similar to each other (Average Dice: 0.38). There was no similarity between impulsivity- and hypomania- related networks (Table 4). Taken together, we showed that *(i)* the two VOIs related to impulsivity scores exclusively resemble similar intrinsic functional networks; *(ii)* the four VOIs related to hypomania scores exclusively resemble similar intrinsic functional networks; and *(iii)* intrinsic functional networks of impulsivity-related VOIs are spatially different from those of hypomania-related VOIs.

Discussion

Our findings demonstrated a positive association between the impulsivity scores and neural metabolism in the medial part of the right superior frontal gyrus, right middle frontal gyrus, and ACC. In addition, we observed a positive link between the hypomania scores and the neural metabolism in the right superior frontal gyrus, right middle frontal gyrus, right precentral gyrus, and right paracentral lobule (Fig. 1a, b; Table 2). The right middle frontal gyrus was the only region in which the neural correlates of both impulsivity and hypomania overlap (Fig. 2a; Table 3). Moreover, regions exclusively associated with impulsivity were located in the medial part of the right superior frontal gyrus, whereas regions exclusively associated with hypomania were found in the right superior frontal gyrus, right precentral gyrus, and right paracentral lobule (Fig. 2b, c; Table 3). The follow-up FC analysis indicated that the regions exclusively associated with impulsivity and hypomania are parts of distinct intrinsic functional networks (Fig. 3). Dice coefficient analyses demonstrated that intra-group similarities were higher than inter-group ones (Table 4).

Neural metabolism related to impulsivity

Our findings suggest that metabolism in the medial part of the superior frontal gyrus, middle frontal gyrus, and ACC are involved in impulsivity (Figs. 1a and 2b; Tables 2 and 3). These findings are consistent with previous studies reporting the mPFC and ACC play a role in impulse control behaviors in healthy individuals and patients with mental illnesses (Bechara 2005; Bechara and Van Der Linden 2005). For example, it has been reported that the

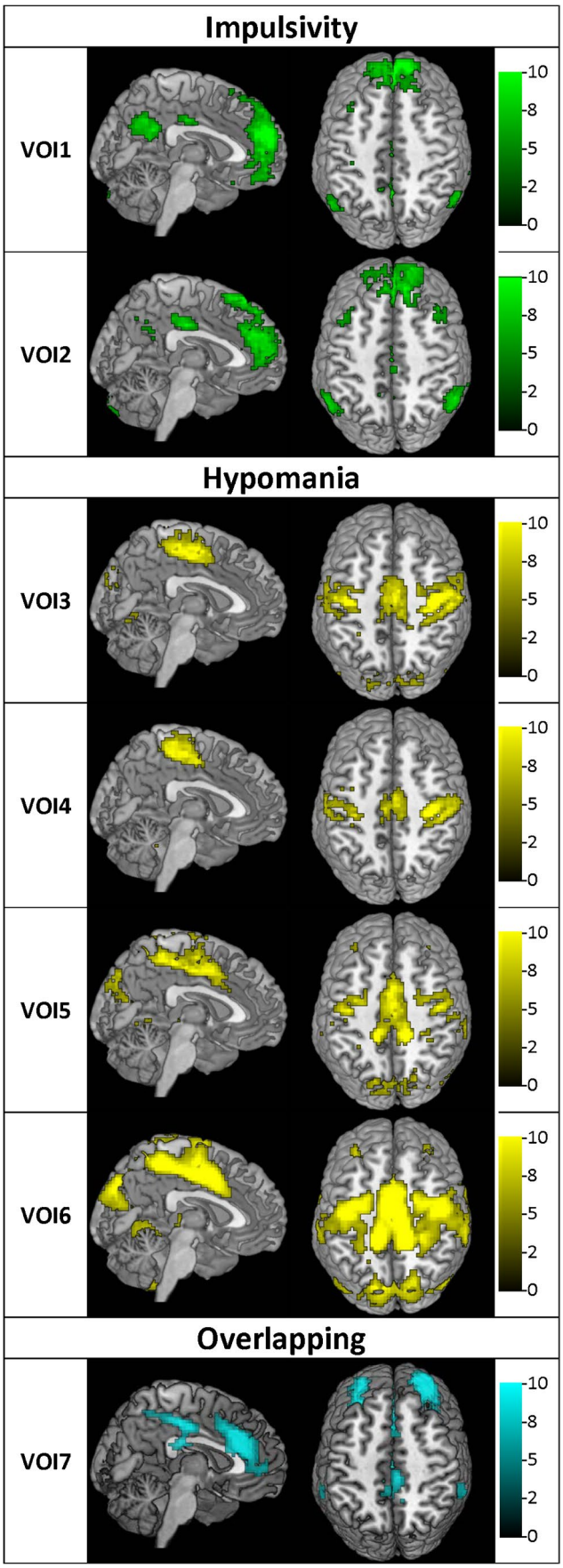

Fig. 3 Voxel-wise functional connectivity patterns for each of the six exclusive seeds for impulsivity and hypomania and one overlapping seed on the dataset of 198 healthy subjects (family-wise error $p < 0.05$, controlled for age and gender)

grey matter volume of the mPFC, OFC, ACC, and insula is correlated with BIS-11 scores (e.g. non-planning and attention/cognitive BIS-11 scores) in healthy participants (Matsuo et al. 2009; Choe et al. 2013). Boes and colleagues also showed that the volume of right ventromedial PFC was a significant predictor of impulse control level in healthy boys (Boes et al. 2009).

Higher impulsivity is often observed in a number of psychiatric disorders including borderline personality disorder, bipolar disorder, attention deficit hyperactivity disorder, and substance abuse disorder (Berlin et al. 2005; Jentsch and Taylor 1999; Newman and Meyer 2014; Winstanley et al. 2006), mainly due to a dysfunction of the prefrontal cortex and basal ganglia (Kim and Lee 2011; Sebastian et al. 2014). It has been reported that impulsivity in cocaine-dependent individuals correlates with lower grey matter volume in the right OFC, left precentral gyrus, and right superior frontal gyrus (Crunelle et al. 2014). Also, subjects with internet gaming addiction showed hyperactivity during No-Go trials in the left superior medial frontal gyrus, right ACC, right superior and middle frontal gyri, left inferior parietal lobule, left precentral gyrus, left precuneus and cuneus. Interestingly, activation of the left superior medial frontal gyrus was positively linked with the BIS-11 scores (Ding et al. 2014). Few studies in PD patients revealed the ventral striatum, ventrolateral PFC, ACC, and amygdala, as being involved in the development of impulsive behaviors and ICDs (Cilia et al. 2008; Cilia and van Eimeren 2011; van Eimeren et al. 2009). In particular, it has been demonstrated that PD patients with pathological gambling had DRT-induced lower regional cerebral blood flow (rCBF) in areas that are implicated in impulse control and response inhibition including the lateral OFC, rostral ACC, amygdala, external pallidum compared to non-gambler PD patients. Moreover, these rCBF alterations showed a positive correlation with DRT-induced changes in gambling severity (van Eimeren et al. 2010). This suggests that DRT induces an abnormal neuronal pattern in PD patients with ICDs, which are similar to those found in non-Parkinsonian pathological gambling and drug addiction. Recently, we have shown that high impulsivity scores in PD are associated with increased neural metabolism within the fronto-insular network including the OFC, ACC, mPFC and insula, which are key areas for proper impulse inhibition (Tahmasian et al. 2015c).

Table 4 DICE coefficients between impulsivity exclusive regions (Volumes of interest (VOIs) 1–2)), hypomania exclusive regions (VOIs 3–6), and overlapping region (VOI 7)

	VOI 1	VOI 2	VOI 3	VOI 4	VOI 5	VOI 6	VOI 7
VOI 1		0.47	0.00	0.00	0.00	0.00	0.08
VOI 2			0.00	0.00	0.00	0.00	0.17
VOI 3				0.65	0.39	0.32	0.00
VOI 4					0.24	0.21	0.00
VOI 5						0.47	0.06
VOI 6							0.08
VOI 7							

Neural metabolism related to hypomania

In our findings, higher levels of self-reported hypomanic symptoms were related to increased metabolic activity of the right superior frontal gyrus, right precentral gyrus, supplementary motor area (SMA) and right paracentral lobule (Figs. 1b and 2c; Tables 2 and 3). An early fMRI study in patients with bipolar disorder showed that patients have more activation in the M1 and SMA during a reaction time task. Such findings, similar to ours, support the important role of the right frontal lobe in mania and mood regulation (Caligiuri et al. 2004). In another neuroimaging study, Yang and colleagues investigated the intrinsic regional homogeneity of patients with depression and screened based on the Hypomania Checklist (HCL-32) (Angst et al. 2005). The results indicated a higher ReHo in the right medial superior frontal cortex, left inferior parietal cortex, and middle/inferior temporal cortex, as well as less ReHo in the left postcentral cortex and cerebellum in the subjects who screened positive on the HCL-32 for bipolar disorder compared to subjects who scored below the published cut-off (Yang et al. 2016).

Our findings are in line with a previous study in PD patients which reported that hypomanic states after DBS were related to increased rCBF mainly in the right hemisphere including the mPFC, primary motor area (M1), globus pallidus, paracentral, and bilateral dorsal ACC. The authors concluded that a higher rCBF in the right M1 during hypomania is not related to movement per se, as auditory stimuli resulted in right-handed movement in both manic and euthymic patients (Ulla et al. 2011). The authors suggested that post-DBS hypomania is mediated by the substantia nigra's effect on the ACC and support for the important role of the basal ganglia on the limbic regions and modulation of mood. In a case-report, it has been suggested that DBS-induced hypomania might be linked to the regulatory system of the associative and limbic cortico-subcortical circuits (Kim et al. 2012). Coenen and colleagues showed that DBS-induced reversible hypomania might be due to activation of the medial forebrain bundle using a diffusion tensor imaging approach in 6 severe PD patients (Coenen et al. 2009), which is a key structure of the mesolimbic- dopamine circuit, a system related to reward system affective disorders, drug addiction, and learning (Ikemoto 2010).

It has been reported that levodopa-induced dyskinesia (LID) is significantly associated with DRT-related hypomania in PD (Maier et al. 2014). Recently, we have shown a positive correlation between impaired self-awareness of LID and glucose metabolism in the mid-cingulate and paracentral gyrus, putamen, SMA, and olfactory gyrus in the same sample (Maier et al. 2016). The above-mentioned studies highlight the role of the superior frontal gyrus, precentral gyrus, SMA and the right paracentral lobule in the pathophysiology of hypomania in PD.

Similarities between neural metabolism related to impulsivity and hypomania

Overlapping regions between the neural metabolism related to impulsivity and hypomania were found in the right PFC, particularly the right middle frontal gyrus (Fig. 2a; Table 3). Several previous neuroimaging studies in bipolar disorder, mania, and impulsivity support this finding and highlight the role of right PFC in such disorders (Townsend et al. 2013; Trost et al. 2014; Fleck et al. 2011; Mitchell and Potenza 2014; Strakowski et al. 2008). The right middle frontal gyrus is a region associated with high-level executive functions, reorienting attention, and also perceptual go/no-go decision-related processes (Talati and Hirsch 2005; Japee et al. 2015). This region could be a potential target for interventions including transcranial direct-current stimulation and transcranial magnetic stimulation to reduce impulsivity and hypomania behaviors (Kuo et al. 2014; Tracy et al. 2015).

Intrinsic functional networks involved in impulsivity and hypomania

Our FC analyses indicated that the regions exclusive to impulsivity and hypomania are parts of specific distinct intrinsic functional networks (Fig. 3). In particular, impulsivity-related seeds are parts of the anterior default mode network (DMN), which is an important neural network activated during rest and deactivated during external and goal-directed executive tasks (Buckner et al. 2008). Abnormalities

of the DMN have been widely reported in depression, bipolar disorder, and impulsivity (Ongur et al. 2010; Inuggi et al. 2014; Manoliu et al. 2013; Zhu et al. 2015). In a recent study with fMRI, Xu and colleagues reported more activation of the anterior DMN while subjects made decisions about their present and more activation of the posterior DMN when subjects made decisions regarding their future. The authors also observed lower FC between the anterior and posterior parts of DMN when participants think about their future rather than other conditions (Xu et al. 2016). Also, within-network and between-network FC alteration of the DMN and salience network in patients with alcohol dependence and such changes were linked with the impulsivity levels of subjects (Zhu et al. 2015). Similar to our findings, several rs-fMRI and task fMRI studies revealed that the DMN's FC is disrupted in PD (see (Tahmasian et al. 2015a) for review). Our recent neuroimaging meta-analysis demonstrated that the posterior part of inferior parietal lobule, which is the main hub of the DMN is disrupted across previous rs-fMRI studies in PD (Tahmasian et al. 2017). Task-based and resting-state connectivity analyses using two independent healthy individual data sets revealed convergent aberrations formed an interconnected network mainly in the DMN (Tahmasian et al. 2017).

Other sets of FC analyses indicated that the regions exclusive to hypomania are parts of particular intrinsic functional networks, mainly located in the dorsomedial PFC, superior frontal gyrus, right precentral gyrus, SMA and right paracentral lobule, bilateral insula, and rolandic operculum. The dorsal nexus and fronto-insular cortex are important regions in the pathophysiology of mood disorders (Langan and McDonald 2009; Sheline et al. 2010). Finally, yet importantly, FC patterns of impulsivity seeds are statistically different from those of hypomania seeds in healthy brains, reflecting the distinct intrinsic functional networks involved in impulsive and hypomanic symptoms. It is worthy to note that we chose a dataset from young healthy subjects to map the fundamental intrinsic functional connectivity patterns of our seeds.

Strengths, limitations, and future directions

Our findings shed new light on the complexity of two common neuropsychiatric characteristics of PD. In future, this might help to choose better targeted treatment strategies for patients who present high impulsivity or self-reported hypomanic symptoms before initiation of DRT or DBS to prevent acceleration of these into ICDs and clinically relevant mania. Moreover, our results revealed that although impulsivity and hypomanic symptoms could be very similar in clinical presentation, they are correlated with distinct intrinsic neural networks. One should note that our findings are based on moderate levels of impulsivity and hypomania in this small sample. Thus, these findings do not represent necessarily the functional regions related to ICDs or mania, rather they reflect potential regions associated with development of such disorders in PD patients.

Furthermore, it has been discussed that DRT is an important confounding factor in functional brain organization in PD (Tahmasian et al. 2015a; van Eimeren et al. 2010). ICDs may occur due to an overstimulation of the mesolimbic system by DRT in PD (Voon et al. 2011a, b). Also, DRT-related hypomania has been shown to be associated with higher LEDD, younger age, and dyskinesia (Maier et al. 2014). Therefore, we controlled for influences of medication (LEDD for dopamine agonists), age, gender, and dyskinesia on local FDG metabolism, although our PD patients had the same dopaminergic state during the behavioral and imaging examinations.

Several limitations of this study should be noted. First, the BIS-11 and SMRI scales are self-reported and although they are the most commonly used impulsivity and hypomania questionnaires, they reflect the subjective view of subjects toward themselves. Especially with regards to impulsivity, it might be of interest to look also at behavioral indicators of impulsivity in cognitive tests (e.g. false alarms). Second, the current data reflects moderate levels of impulsivity or hypomania in our patients and therefore cannot be generalized to patients with ICDs or clinically diagnosed manic states. Third, the number of our participants was limited, and we did not include an elderly healthy control group to compare the results with them. Forth, while no scale assessing current (hypo) manic symptoms have been validated outside the research focusing on mood disorders, there is evidence that they are associated with other indicators of mania supporting their validity. While it is a limitation that the scale has not been validated in PD before, our current and previous data (Tahmasian et al. 2015c) show that it can used and allows to track changes in such symptoms in PD although they do not have a diagnosis of bipolar disorder. Another limitation is that this study evaluated patients under daily medication, which can influence functional brain organization (Tahmasian et al. 2015a). Of note, creating VOIs from the correlations between FDG-PET and hypomania and impulsivity measures in PD patients and applying them to FC patterns in an independent group of healthy adults does not directly speak to alterations in the intrinsic neural network associated with impulsivity and hypomania in PD patients. Hence, future studies using multimodal imaging (e.g. simultaneous PET/MRI) with larger sample size should systematically compare healthy controls and PD patients with and without mania and ICDs.

Conclusions

Our findings shed new light on the neural correlates of impulsivity and hypomania in PD. In summary, the current study provides evidence that there are similarities and differences between impulsivity-related and hypomania-related glucose metabolism in PD. In particular, activity in the middle frontal gyrus is linked with both impulsivity and hypomania. We found exclusive regions for impulsivity in the medial part of the right superior frontal gyrus and exclusive regions for hypomania in the right superior frontal gyrus, right precentral gyrus and right paracentral lobule. FC patterns of the two impulsivity-related seeds are different from the four hypomania-related seeds identified in healthy brains, suggesting that intra-group similarities were higher than inter-group ones. This data is consistent with several neuroimaging studies, suggesting the important role of PFC in both hypomania and impulsivity.

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Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval Registration and ethical approval conforming to Human Research Committee guidelines was obtained by the medical ethics board of the University Hospital of Cologne (EK 10-278).

Informed consent Written informed consent was obtained from all participants included in this study.

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